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(54) **Bis(hydroxymethyl)cyclopropylmethyl pyrimidine derivatives, their preparation and their use as anti-viral agents**

Bis(hydroxymethyl)cyclopropylmethyl Pyrimidin Derivate, deren Herstellung und deren Verwendung als anti-virale Mittel

Dérivés de bis (hydroxyméthyl)cyclopropylméthyl pyrimidine, leur préparation et leur utilisation comme agents anti-viraux

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(73) Proprietor: **Ajinomoto Co., Inc.**
Tokyo 104 (JP)

(72) Inventors:
- **Onishi, Tomoyuki, c/o Central Research Lab.**
  Kawasaki-ku, Kawasaki-shi, Kanagawa-ken (JP)
- **Mukai, Chika, c/o Central Research Lab.**
  Kawasaki-ku, Kawasaki-shi, Kanagawa-ken (JP)
- **Sekiyama, Takaaki, c/o Central Research Lab.**
  Kawasaki-ku, Kawasaki-shi, Kanagawa-ken (JP)
- **Tsuji, Takashi, c/o Central Research Lab.**
  Kawasaki-ku, Kawasaki-shi, Kanagawa-ken (JP)
- **Iwayama, Satoshi, c/o Central Research Lab.**
  Kawasaki-ku, Kawasaki-shi, Kanagawa-ken (JP)
- **Okunishi, Masahiko, c/o Central Research Lab.**
  Kawasaki-ku, Kawasaki-shi, Kanagawa-ken (JP)

(74) Representative: **Nicholls, Kathryn Margaret et al**
MEWBURN ELLIS York House 23 Kingsway
London WC2B 6HP (GB)

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] The present invention relates to cyclopropane derivatives having an anti-viral activity especially effective against varicella-zoster viruses and herpes simplex viruses, and also to anti-viral agents containing the same.

[0002] Varicella-zoster viruses cause varicella in infants with high fever and cause zoster in adults with much pain such as neuralgia, etc. Some anti-viral agents such as acyclovir and the like are used but are not always satisfactory in view of their pharmaceutical potency and unfavourable side-effect (Am. J. Med., 85, (Suppl. 2A), 116-122 (1988), JP-A-56/87599, JP-A-5/78357).

[0003] Embodiments of the present invention desirably provide compounds having high anti-viral potency against varicella-zoster virus and having high safety.

[0004] EP-A-0 484 843 discloses an optically active cyclobutyl pyrimidine, in which the pyrimidine nucleus carries a 2-bromoethenyl group at the 5 position. The compound is active against herpes simplex virus 1 and varicella-zoster virus.

[0005] J. Med. Chem. (1992), 35(10), pp1799-1806 relates to cyclobutyl compounds carrying a halovinyluracil group. The compounds are said to have excellent activity against varicella-zoster virus.

[0006] EP-A-0 502 690 discloses cyclopropane derivatives for use as antivirals. Some of these are thymine derivatives, in which the pyrimidine nucleus has a methyl group at the 5 position.

[0007] J. Med. Chem. (1988), 31(11), pp2304-2315 describes the synthesis and antiherpetic activity of 9-[[(Z)-2-(hydroxymethyl) cyclopropyl]methyl] guanine and related compounds. Some compounds include thymine in place of guanine.

[0008] EP-A-0 291 230 discloses 1-[2, (hydroxymethyl)cycloalkylmethyl]-5-substituted uracils as inhibitors of herpes simplex virus thymidine kinase inhibitors. In each case the cycloalkyl group is a cyclobutyl group or larger ring.

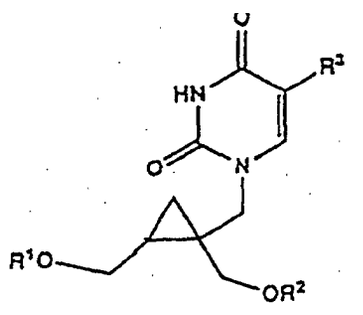
[0009] EP-A-0 458 363 discloses fluorinated cyclobutyl compounds in which the ring carries either a purine or pyrimidyl residue. The compounds are antivirals.

[0010] The present inventors have found that the following cyclopropane derivatives have an excellent anti-viral activity against varicella-zoster viruses and herpes simplex viruses:

(i) 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl] methyl-5-[(E)-2-chloroethenyl]-2,4(1H,3H)-pyrimidinedione;
(ii) 1-[1'S, 2'R-bis (hydroxymethyl)cyclopropan-1'-yl] methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione;
(iii) 1-[1'S, 2'R-bis (hydroxymethyl)cyclopropan-1'-yl] methyl-5-[(E)-2-iodoethenyl]-2,4(1H,3H)-pyrimidinedione;
(iv) 1-[1'α, 2'β-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione;

wherein each hydroxyl group independently is optionally in the form of an ester with an acyl group having 1 to 6 carbon atoms, or with an acyl group having 1 to 6 carbon atoms substituted with a cycloalkyl group or aryl group; and pharmaceutically acceptable salts thereof.

[0011] For simplicity, the compounds are represented herein by the following general formula (I) which does not indicate the stereochemistry of the compounds at the cyclopropane ring:



(I)

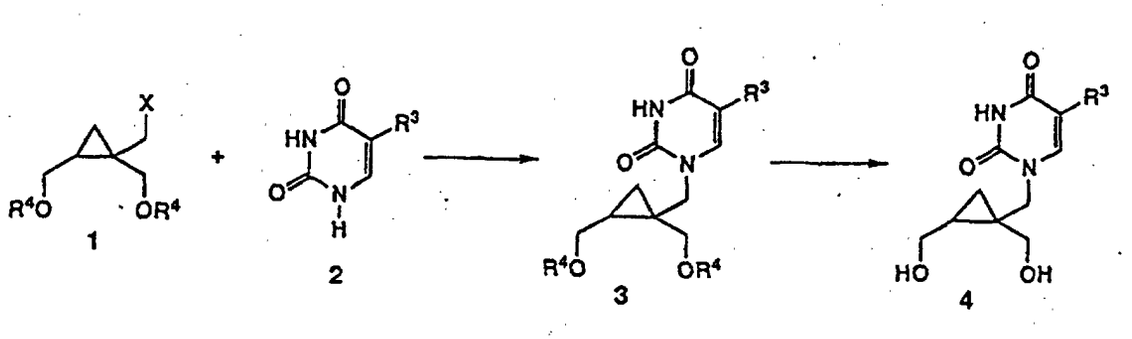
wherein R^1 and R^2, which may be the same or different, each represent a hydrogen atom or an acyl group; and R^3 represents the appropriate (E)-2-haloethenyl group.

[0012] In formula (I), the acyl group represented by R^1 and R^2 is an acyl group which can be derived from fatty acids having 1 to 6 carbon atoms, for example, including formyl, acetyl, propionyl, butyryl, valeryl, isovaleryl, pivalyl, hexanoyl group. The acyl group may be substituted with a cycloalkyl group or an aryl group, for example, including cyclohexanecarbonyl, or benzoyl groups.

[0013] Regarding the relative configuration of each compounds, the cyclopropane moiety is considered to be on a flat plane and the substituents positioned below the plane are represented by "α" while those positioned above the

same by "β".

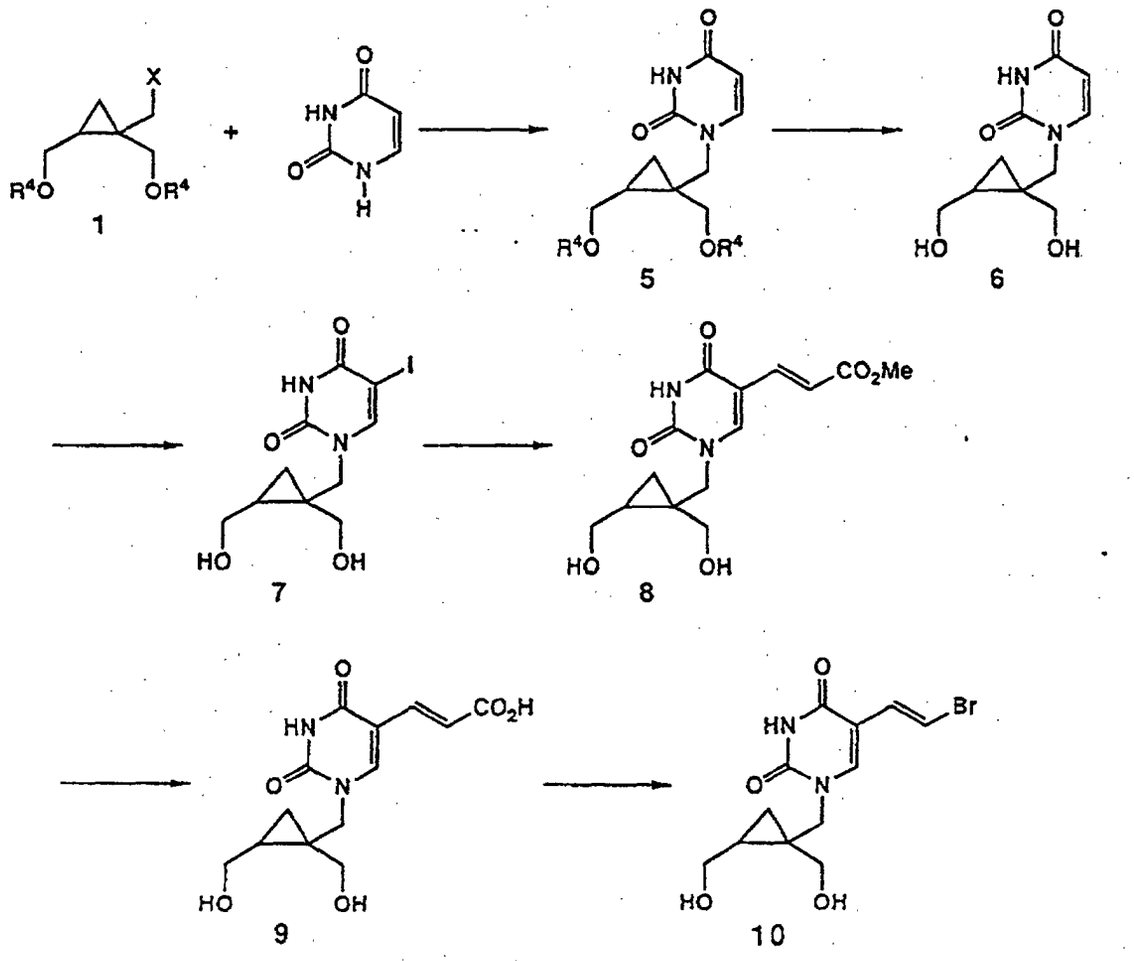
[0014] The compounds of the present invention may be prepared, for example, as follows:



[0015] Wherein R^4 represents a protective group for a hydroxyl group; X represents a leaving group such as a p-toluenesulfonyloxy group, methanesulfonyloxy group or a halogen, etc.; and R^3 has the same meaning as mentioned above.

[0016] Precisely, a compound of formula (1), which may be prepared according to the method described in Japanese Patent Laid-Open Application No. 5-78357, is reacted with a 5-substituted uracil of formula (2) in a polar solvent such as dimethylsulfoxide, dimethylformamide, etc., in the presence of a base such as potassium carbonate or sodium hydride, by stirring them under heat, to give a compound of formula (3). In this step, 18-crown-6 may be added to the reaction system. Next, the protective group R^4 is removed to obtain a compound of formula (4).

[0017] On the other hand, 1-[1'S,2'R-bis(hydroxymethyl) cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H, 3H)-py rimidinedione, which is within the scope of the compounds of the present invention, may also be produced according to the following process.



Wherein R^4 and X have the same meanings as those mentioned above.

[0018] Precisely, a compound of formula (1) is reacted with uracil in a polar solvent such as dimethylsulfoxide, dimethylformamide, etc., in the presence of a base such as potassium carbonate or sodium hydride, by stirring them under heat, to give a compound of formula (5). In this step, 18-crown-6 may be added to the reaction system. Next, the protective group R^4 is removed to obtain a compound of formula (6), and this is iodinated by treating it with iodine and an aqueous solution of nitric acid in dioxane, to obtain a compound of formula (7). This is then treated with methyl acrylate in the presence of palladium(II) acetate, triphenylphosphine and triethylamine in dioxane to give a compound of formula (8), which is thereafter saponified at its methyl ester group to obtain a compound of formula (9). The compound of formula (9) thus obtained is treated with N-bromosuccinimide in the presence of potassium bicarbonate or the like in a polar solvent such as dimethylformamide, etc. to obtain a compound of formula (10).

[0019] Where the compounds of the present invention are used as anti-viral agents, they may be applied to patients by intravenous administration, peroral administration or subcutaneous administration. The dose of the compound varies, depending on the condition and the age of the patient and on the way how to administer the compound to the patient. In general, it is from 0.1 to 500 mg/kg/day. The compounds of the present invention are mixed with suitable pharmaceutical carriers to form anti-viral compositions, which are administered to patients. As the forms of the anti-viral compositions, for example, mentioned are injection, tablets, granules, fine granules, powder, capsules, cream, suppositories, etc. As the pharmaceutical carriers, for example, mentioned are lactose, glucose, D-mannitol, starch, crystalline cellulose, calcium carbonate, kaolin, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, ethanol, carboxymethyl cellulose, calcium carboxymethyl cellulose, magnesium stearate, talc, acetyl cellulose, white sugar, titanium oxide, benzoic acid, paraoxybenzoate, sodium dehydroacetate, arabic gum, tragacanth, methyl cellulose, egg yolk, surfactants, simple syrup, citric acid, distilled water, glycerin, propylene glycol, macrogol, sodium monohydrogenphosphate, sodium dihydrogenphosphate, sodium phosphate, sodium chloride, phenol, salomethyl, sodium hydrogensulfite, etc. These are mixed with the compounds of the present invention to form various forms of pharmaceutical preparations.

[0020] The content of the active ingredient of the present invention in the anti-viral composition of the invention

greatly varies, depending on the form of the pharmaceutical composition, and therefore is not specifically defined. In general, however, it may be from 0.01 to 100 % by weight, preferably from 2 to 100 % by weight, relative to the total weight of the composition.

Examples:

[0021] Next, the present invention will be explained in more detail by means of the following examples.

Example 1:

[0022] Preparation of (1R,7R)-1-bromomethyl-4,4-diphenyl-3,5-dioxabicyclo[5.1.0] octane

Step 1:

Preparation of ethyl (1S,5R)-3-oxa-2-oxobicyclo[3.1.0]hexane-1-carboxylate:

[0023] 2.42 g (105 mmol) of metallic sodium were dissolved in 200 ml of ethanol at 0 °C under argon atmosphere. To this solution, added were 16.7 g (110 mmol) of diethyl malonate; and 7.8 ml (100 mmol) of R-(-)-epichlorohydrin dissolved in 5 ml of ethanol were dropwise added thereto at room temperature. The resulting solution was heated at 75 °C for 20 hours and then cooled to 0 °C, and the precipitates thus formed were removed by filtration. The resulting filtrate was concentrated under reduced pressure, and water was added to the residue, which was then extracted with dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and then the solvent was removed therefrom by distillation. The thus-obtained residue was subjected to silica gel chromatography (hexane:ethyl acetate = 5:1 to 1:1) to obtain 12.0 g (70 mmol, 70 %) of the entitled compound. This was colorless oil and had the following physical data:
^{1}H-NMR($CDCl_3$)δ: 1.31 (t, J=7.1Hz, 3H), 1.37 (dd, J=4.8, 5.4Hz, 1H), 2.08 (dd, J=4.8, 8.0Hz, 1H), 2.72 (m, 1H), 4.18 (d, J=9.6Hz, 1H), 4.27 (q, J=7.1Hz, 2H), 4.36 (dd, J=4.5, 9.6Hz, 1H); FD mass: 170(M^+)

Step 2:

Preparation of ethyl (1S,2R)-1,2-bis(hydroxymethyl)cyclopropanecarboxylate:

[0024] 12.0 g (70 mmol) of ethyl (1S,5R)-3-oxa-2-oxobicyclo[3.1.0]hexane-1-carboxylate were dissolved in 200 ml of ethanol, and 2.0 g (53 mmol) of sodium borohydride were added thereto. This solution was stirred for 2 hours at room temperature, and then 27 ml of 2 N-hydrochloric acid and 100 ml of ethyl acetate were added thereto. The precipitates thus formed were removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, which was the extracted with dichloromethane. The thus-obtained organic layer was dried with anhydrous sodium sulfate, and the solvent was removed therefrom by distillation. The thus-obtained oily residue was subjected to silica gel chromatography (dichloromethane:methanol = 25:1) to obtain 8.35 g (48 mmol, 69 %) of the entitled compound. This was colorless oil and had the following physical data:
^{1}H-NMR($CDCl_3$)δ: 0.76 (dd, J=4.8, 6.6Hz, 1H), 1.27 (t, J=7.2Hz, 3H), 1.49 (dd, J=4.8, 9.0Hz, 1H), 2.05 (m, 1H), 3.23 (d, J=12.8Hz, 1H), 3.33 (dd, J=11.1, 12.5Hz, 1H), 4.08 (dd, J=5.1, 12.5Hz, 1H), 4.17 (q, J=7.2Hz, 2H), 4.52 (d, J=12.8Hz, 1H); FD mass 175 (MH^+)

Step 3:

Preparation of ethyl (1R,7R)-4,4-diphenyl-3,5-dioxabicyclo[5.1.0]octyl-1-carboxylate:

[0025] 6.81 g (30 mmol) of (1S,2R)-2,3-dichloro-5,6-dicyano-1,4-benzoquinone were dissolved in 250 ml of 2-dichloroethane, and a solution prepared by dissolving 5.23 g (30 mmol) of ethyl 1,2-bis(hydroxymethyl)cyclopropane-carboxylate obtained in the previous step 2 in Example 1 and 5.83 g (30 mmol) of diphenyldiazomethane in 130 ml of 1,2-dichloroethane was gradually and dropwise added thereto and thereafter stirred for one hour at room temperature. The resulting solution was concentrated under reduced pressure and then dissolved in toluene. The toluene solution was washed with a saturated aqueous solution of sodium hydrogencarbonate and dried with anhydrous sodium sulfate, and thereafter the solvent was removed therefrom by distillation under reduced pressure. The thus-obtained residue was subjected to silica gel chromatography (dichloromethane) to obtain 8.72 g (25.77 mmol, 85 %) of the entitled compound. This was yellow oil and had the following physical data:
^{1}H-NMR($CDCl_3$)δ: 1.22 (t, J=7.0Hz, 3H), 1.33 (dd, J=3.6, 7.1Hz, 1H), 1.43 (dd, J=3.6, 9.3Hz, 1H), 1.8 (m, 1H), 3.68

(d, J=13.3Hz, 1H), 3.76 (dd, J=3.1, 12.9Hz, 1H), 4.1 (m, 3H), 4.65(d, J=13.0Hz, 1H), 7.2-7.6 (m, 10H); FD mass: 338 (M^+)

Step 4:

Preparation of (1S,7R)-4,4-diphenyl-3,5-dioxabicyclo [5.1.0]octyl-1-methanol:

[0026] 7.01 g (20.7 mmol) of ethyl (1R,7R)-4,4-diphenyl-3,5-dioxabicyclo[5.1.0]octyl-1-carboxylate were dissolved in 10 ml of dry tetrahydrofuran, and 12 ml of 2 M lithium borohydride/tetrahydrofuran solution were added thereto and stirred for 16 hours at 72 °C underin an argon atmosphere. After this was cooled to 0 °C, a saturated aqueous solution of ammonium chloride was added thereto. Then, this was extracted with ethyl acetate. The organic layer was washed with water and dried with anhydrous sodium sulfate, and then the solvent was removed therefrom by distillation. The thus-obtained residue was subjected to silica gel chromatography (dichloromethane:methanol = 19:1) to obtain 5.54 g (18.7 mmol. 90 %) of the entitled compound. This was white solid, having a melting point of 93 °C and the following physical data:
^{1}H-NMR($CDCl_3$)δ: 0.67 (dd, J=4.4, 8.9Hz, 1H), 0.96 (dd, J=4.4, 5.8Hz, 1H), 1.08 (m, 1H), 3.42 (dd, J=11.0, 27.9Hz, 2H), 3.65 (dd, J=3.9, 12.9Hz, 1H), 3.76 (d, J=12.7Hz, 2H), 4.1 (m, 2H), 7.2-7.6 (m, 10H); FD mass:296 (M^+)

Step 5:

Preparation of (1R,7R) -1-bromomethyl-4,4-diphenyl-3,5-dioxabicyclo[5.1.0]octane:

[0027] 5 g (16.87 mmol) of (1S,7R)-4,4-diphenyl-3,5-dioxabicyclo[5.1.0] octyl-1-methanol were dissolved in 100 ml of 1,2-dichloroethane, and 1.2 ml (8.4 mmol) of triethylamine, 7.97 g (30.4 mmol) of triphenylphosphine and 10.1 g (30.4 mmol) of carbon tetrachloride were added thereto and stirred for 20 minutes. To this, added was a saturated aqueous solution of sodium hydrogencarbonate, and the resulting mixture was extracted with hexane. The organic layer was washed with water and dried with anhydrous sodium sulfate, and then the solvent was removed therefrom by distillation under reduced pressure. The thus-obtained residue was subjected to silica gel chromatography (hexane: ethyl acetate = 3:1) to obtain 5.45 g (15.1 mmol, 90 %) of the entitled compound. This was yellow oil and had the following physical data:
^{1}H-NMR($CDCl_3$)δ: 0.83 (dd, J=4.2, 8.5Hz, 1H), 1.16-1.28 (m, 2H), 3.13 (d, J=10.2Hz, 1H), 3.60 (dd, J=3.5, 12.9Hz, 2H), 3.80 (d, J=12.9Hz, 1H), 4.07 (dd, J=4.8, 13.0Hz, 2H), 7.2-7.6 (m, 10H); FD mass: 358(M^+)

Example 2

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-chloroethenyl]-2,4(1H,3H)-pyrimidinedione:

[0028] 311 mg (0.866 mmol) of (1R,7R) -1-bromomethyl-4,4-diphenyl-3,5-dioxabicyclo[5.1.0]octane prepared according to Example 1 was dissolved in 14.6ml of dimethylformamide, and 150 mg (0.869 mmol) of 5-[(E)-2-chloroethenyl]-2,4(1H,3H)-pyrimidinedione, 120 mg (0.868 mmol) of potassium carbonate and 191 mg (0.723 mmol) of 18-crown-6 were added thereto. After stirring for 1.5 hours at 60°C, the mixture was cooled to room temperature and insoluble substances were removed therefrom by filtration. The filtrate was concentrated under reduced pressure, and 7 ml of methanol and 3.3 ml of 1 N-hydrochloric acid were added thereto. After the mixture was stirred for 20 minutes at room temperature, and methanol was removed therefrom by distillation under reduced pressure. This was adjusted to have pH 4, by adding potassium carbonate thereto, and subjected to reversed-phase C18 silica gel chromatography (water: methanol=8:2) to obtain 108 mg (0.378 mmol, 51%) of the entitled compound. This was colorless solid and had the following physical data:

^{1}H-NMR(CD_3OD)δ : 0.56(t, J=5.4Hz, 1H), 1.01(dd, J=5.4, 8.7Hz, 1H), 1.38-1.49(m, 1H), 3.45(dd, J=9.3, 12.2Hz, 1H), 3.51(d,J=12.3Hz, 1H), 3.76(d, J=12.3Hz, 1H), 3.81(d, J=14.4Hz, 1H), 3.88(dd, J=5.9, 12.2Hz, 1H), 3.92(d, J=14.4Hz, 1H), 6.56(d, J=13.4Hz, 1H), 7.26(d, J=13.4Hz, 1H), 7.78(s,1H): High resolution mass spectrum ($C_{12}H_{16}ClN_2O_4$, M+H):

calculated value:287.0799

measured value:287.0812

Example 3

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione:

[0029] 71.1 mg (198 μmol) of (1R,7R) -1-bromomethyl-4,4-diphenyl-3,5-dioxabicyclo[5.1.0]octane prepared according to Example 1 was dissolved in 4ml of dimethylformamide, and 42.9 mg(198 μmol) of 5-[(E)-2-bromoethenyl]-2,4 (1H,3H)-pyrimidinedione, 27.4 mg (198 μmol) of potassium carbonate and 52.3 mg (198 μmol) of 18-crown-6 were added thereto. After stirring for 2 hours at 60°C, the mixture was cooled to room temperature and insoluble substances were removed therefrom by filtration. The filtrate was concentrated under reduced pressure, and 2 ml of methanol and 0.5 ml of 2 N-hydrochloric acid were added thereto. After the mixture was stirred for 30 minutes at room temperature, and methanol was removed therefrom by distillation under reduced pressure. This was adjusted to have pH 4, by adding potassium carbonate thereto, and subjected to reversed-phase C18 silica gel chromatography (water:methanol≈7:3) to obtain 13.0 mg (39.3 μmol, 20%) of the entitled compound. This was colorless solid and had the following physical data:

[0030] ^{1}H-NMR(DMSO-d_6)δ :0.42(t, J=5.4Hz, 1H), 0.80(dd, J=4.8, 8.7Hz, 1H), 1.20-1.30(m, 1H), 3.24-3.37(m, 2H), 3.50(dd, J=6.0, 12.0Hz, 1H), 3.61(dt, J=12.0, 6.0Hz, 1H), 3.61(d, J=14.1Hz, 1H), 3.77(d, J=14.1Hz, 1H), 4.50-4.59(m, 2H), 6.81(d, J=13.5Hz, 1H), 7.23(d, J=13.5Hz, 1H), 7.91(s, 1H): High resolution mass spectrum ($C_{12}H_{16}BrN_2O_4$, M+H):

calculated value:331.0293

measured value:331.0298

Example 4:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione:

Step 1:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-2,4(1H,3H)-pyrimidinedione:

[0031] 973 mg (2.26 mmol) of (1R,7R) -1-bromomethyl-4,4- diphenyl-3,5-dioxabicyclo[5,1,0]octane prepared according to Example 1 were dissolved in 5 ml of dimethylsulfoxide, and 304 mg (2.71 mmol) of uracil, 375 mg (2.71 mmol) of potassium carbonate and 597 mg (2.26 mmol) of 18-crown-6 were added thereto. After stirred for 5 days at 100 °C, the mixture was cooled to room temperature and the insoluble substances were removed therefrom by filtration. The filtrate was concentrated under reduced pressure, and 2 ml of methanol and 0.5 ml of 2 N-hydrochloric acid were added thereto. After this was stirred for 30 minutes at room temperature, the methanol was removed therefrom by distillation under reduced pressure. This was adjusted to have pH 4, by adding potassium carbonate thereto, and purified by reversed-phase C18 silica gel chromatography (water:methanol = 8:2) to obtain 113 mg (0.497 mmol, 22 %) of the entitled compound. This was white solid and had the following physical data:

^{1}H-NMR($CDCl_3$)δ:0.55(t, J=5.4Hz, 1H), 1.00(dd, J=5.4, 9.0Hz, 1H), 1.35-1.46(m, 1H), 3.46(dd, J=9.3, 12.0Hz, 1H), 3.49(d, J=12.3Hz, 1H), 3.77(d, J=12.3Hz, 1H), 3.83-3.92(m, 3H), 5.68(d, J=7.8Hz, 1H), 7.69 (d, J=7.8Hz, 1H)

High resolution mass spectrum ($C_{10}H_{15}N_2O_4$, M+H):

calculated value: 227.1032

measured value: 227.1008

Step 2:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-iodo-2,4(1H,3H)-pyrimidinedione:

[0032] 45.0 mg (0.199 mmol) of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-2,4(1H,3H)-pyrimidinedione were dissolved in 4 ml of dioxane, and 102 mg (0.40 mmol) of iodine and 0.267 ml of 0.8 N-nitric acid were added thereto. After stirred for 4 hours at 95 °C, this was cooled to room temperature, and a saturated aqueous solution of sodium thiosulfate was added thereto until the color of the reaction liquid disappeared. The solvent was removed by distillation under reduced pressure, and the residue was subjected to silica gel chromatography (dichloromethane: methanol=19:1) to obtain 33.5 mg (95.5 μmol, 48 %) of the entitled compound. This was white solid and had the following physical data:

^{1}H-NMR($CDCl_3$)δ:0.55(t, J=5.4Hz, 1H), 1.00(dd, J=5.4, 8.7Hz, 1H), 1.36-1.47(m, 1H), 3.45(dd, J=9.0, 11.7Hz, 1H), 3.51(d, J=12.0Hz, 1H), 3.76(d, J=12.0Hz, 1H), 3.86(dd, J=6.3, 11.7Hz, 1H), 3.86(2H, s), 8.17(s, 1H)

High resolution mass spectrum ($C_{10}H_{14}IN_2O_4$, M+H):
calculated value: 352.9998
measured value: 353.0007

step 3:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-methoxycarbonylethenyl]-2,4(1H,3H)-pyrimidinedione:

[0033] Dry dioxane (6.7ml, purified by passage through basic alumina) was deoxygenated. To the deoxygenated were added 45.1 mg (0.201 mmol) of palladium (II) acetate, 104.6 mg (0.399 mmol) of triphenylphosphine, and 556 mg (5.49 mmol) of triethylamine. The mixture was stirred for 40 minutes at 70°C. Then 704 mg (200 mmol) of 1-[1'S, 2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-iodo-2,4(1H,3H)-pyrimidinedione and methyl acrylate (3 56mg, 4.13 mmol) were added thereto, and the mixture was stirred for 3 hours at 70°C. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The mixture was subjected to silica gel chromatography (dichloromethane:methanol=19:1) to obtain 458mg (1.48 mmol, 74%) of the entitled compound. This was yellow solid and had the following data:
^{1}H-NMR(CD_3OD)δ: 0.57(t, J=5.4Hz, 1H), 1.02(dd, J=5.4, 8.7Hz, 1H), 1.41-1.51(m, 1H), 3.45(dd, J=9.5, 11.8Hz, 1H), 3.53(d, J=12.3Hz, 1H), 3.78(d, J=12.3Hz, 1H), 3.78(s, 3H), 3.81(d, J=14.2Hz, 1H), 3.88(dd, J=6.3, 11.8Hz, 1H), 4.01 (d, J=14.2Hz, 1H), 6.96(d, J=15.6Hz, 1H), 7.45(d, J=15.6Hz, 1H), 8.12(s,1H) FAB MASS:311(MH+)

step 4:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-carboxyethenyl]-2,4(1H,3H)-pyrimidinedione:

[0034] 216 mg (0.694 mmol) of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-methoxycarbonylethenyl]-2,4(1H,3H)-pyrimidinedione was dissolved in 1.5 ml of 2N-sodium hydroxide solution. The solution was stirred at room temperature for 45 minutes and then filtered. The filtrate was cooled to 0°C, and stirred for 30 minutes, and was adjusted to have pH 2.0 by adding 6N-hydrochloric acid. The precipicate was filtrated, and washed with cold water, air-dried, and then dried overnight in vacuo at room temperature to obtain 141 mg (0.477 mmol, 69%) of the entitled compound. This was white solid and had the following physical data:
^{1}H-NMR(CD_3OD)δ :0.41 (t, J=5.1Hz, 1H), 0.82(dd, J=5.0, 8.6Hz, 1H), 1.23-1.33(m, 1H), 3.46-3.61(m, 4H), 3.65(d, J=14.1Hz, 1H), 3.82(d,J=14.1Hz, 1H), 4.57(2H, bs), 6.76(d, J=15.8Hz, 1H), 7.27(d, J=15.8Hz, 1H), 8.19(s, 1H), 11.5 (bs, 1H) FAB MASS:297(MH+)

step 5:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione:

[0035] 10.0 mg (0.034 mmol) of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-carboxyethenyl]-2,4(1H,3H)-pyrimidinedione were dissolved in 183 µl of dry dimethylformamide, and 10.3 mg (0.102 mmol) of potassium hydrogen carbonate and 6.8 mg (0.038mmol) N-bromosuccinimide thereto. After stirred for 2.5 hours at room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The mixture was subjected to reversed-phase C18 silica gel chromatography (water:methanol=9:1) to obtain 8.4 mg(0.025 mmol, 75%) of the entitled compound. The 1H-NMR spectrum and FAB MASS spectrum of this compound were completely identical to those of the compound prepared in Example 3.

Example 5:

Preparation of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan -1'-yl]methyl-5-[(E)-2-iodoethenyl]-2,4(1H,3H)-pyrimidinedione:

[0036] 61 mg (0.171 mmol) of (1R,7R)-1-bromomethyl-4,4-diphenyl-3,5-dioxabicyclo[5.1.0]octane prepared as in Example 1 were dissolved in 3.9 ml of dimethylformamide, and 45 mg (0.170 mmol) of 5-[(E)-2-iodoethenyl]-2,4(1H, 3H)-pyrimidinedione, 24 mg (0.174 mmol) of potassium carbonate and 38 mg (0.144 mmol) of 18-crown-6 were added thereto. After stirring for 1.5 hours at 60°C, the mixture was cooled to room temperature and insoluble substances

were removed therefrom by filtration. The filtrate was concentrated under reduced pressure, and 0.52 ml of methanol and 1.0 ml of 1 N-hydrochloric acid were added thereto. After the mixture was stirred for 20 minutes at room temperature, and methanol was removed therefrom by distillation under reduced pressure. This was adjusted to have pH 4 by adding potassium carbonate thereto, and subjected to reversed-phase C18 silica gel chromatography (water: methanol=7:3) to obtain 11.2 mg (29.6 μmol, 26%) of the entitled compound. This was colorless solid and the following physical data: ^{1}H-NMR(CD_3OD)δ :0.56(t, J=5.4Hz, 1H), 1.00(dd, J=5.4, 8.7Hz, 1H), 1.38-1.48(m, 1H), 3.45(dd, J=9.6, 12.3Hz, 1H), 3.51(d,J=12.3Hz, 1H), 3.76(d, J=12.3Hz, 1H), 3.81(d, J=14.6Hz), 3.88(dd, J=5.6, 12.3Hz, 1H), 3.92(d, J=14.6Hz, 1H), 7.16(d, J=14.7Hz, d), 7.34(d, J=14.7Hz, 1H), 7.80(s, 1H): High resolution mass spectrum ($C_{12}H_{16}IN_2O_4$, M+H):

calculated value:379.0155

measured value:379.0156

Example 6:

Preparation of 1-[1'α,2'β-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione:

[0037] 475 mg (0.960 mmol) of (1'α,2'β)-bis(benzoyloxymethyl)cyclopropan-1'-yl]methyl-p-toluenesulfonate was dissolved in 19 ml of dimethylformamide, and 250 mg (1.15 mmol) of 5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione, 159 mg (1.15 mmol) of potassium carbonate and 277 mg (1.15 mmol) of 18-crown-6 were added thereto. After stirring for 12 hours at 60°C, the mixture was cooled to room temperature and insoluble substances were removed therefrom by filtration. The filtrate was concentrated under reduced pressure, and 89.8 μl of sodium methoxide, 28% solution in methanol and 0.9 ml of methanol were added thereto. After the mixture was stirred for 30 minutes at room temperature, 0.44 ml of 1N-hydrochloric acid was added, and methanol was removed therefrom by distillation under reduced pressure. The mixture was subjected to silica gel chromatography (dichloromethane:methanol=13:1) to obtain 27.0 mg (0.082 mmol, 9%) of the entitled compound. This was colorless solid and had the following physical data:
^{1}H-NMR(DMSO-d_6)δ :0.50(t, J=5.1Hz, 1H), 0.58(dd, J=5.1, 8.8Hz, 1H),1.05-1.15(m, 1H), 3.11-3.37(m, 3H), 3.65-3.75 (m,1H), 3.85(d, J=14.6Hz, 1H), 3 .92(d, J=14.6Hz, 1H), 4.55(t, J=5.4Hz, 1H), 4.65(t, J=5.4Hz, 1H), 6.80(d, J=13.7Hz, 1H), 7.22(d, J=13.7Hz, 1H), 7.99(s, 1H), 11.48(bs, 1H)
High resolution mass spectrum ($C_{12}H_{16}BrN_2O_4$, M+H):

calculated value:331.0293

measured value:331.0313

Example 7:

Anti-viral activity against herpes simplex virus:

[0038] The anti-viral activity of the prepared compounds against herpes simplex virus was measured by neutral red dye-uptake method (J. Infect. Dis. 148, 868 (1983)) with modification. Precisely, threefold dilutions of the compounds were prepared in 100 μl volumes of culture medium in the wells of a 96-well culture plate. Sixty microliters of a suspension of Vero cells (3×10^5 cells/ml) were then dispensed into each well. HSV-1 (Tomioka strain) was diluted in medium to approximately 100 $TCID_{50}$/40 μl, as determined by prior titration in a similar dye-uptake assay, and 40 μl of viral suspension were added to the respective wells. Control wells containing no test compound and no virus (cell control) or no cells (blank control) were included in each plate. After 3 days incubation at 37°C in 5 % CO_2 atmosphere, 50 μl of neutral red dye (0.15 % in saline, pH 5.5) was dispensed into each well and the cultures were incubated for a further 45 min at 37 °C. Unincorporated dye was removed by rinsing with PBS. The dye incorporated by viable cells was then eluted into 100 μl per well of citrateethanol buffer (pH 4.2; equal volumes of 0.1 M Sorensen citrate buffer and ethanol); and absorbance at 540 nm of the solution was measured. The absorbance of cell control was assigned 100% and that of blank control was assigned 0%, and the 50% absorbance concentration (ID_{50}) of the test compound was determined. The ID_{50} value of each compound is shown in Table 1. As a comparative compound, acyclovir was used.

Table 1

Test compound	ID_{50} (μg/ml)	Cytotoxity (CD_{50}(μg/ml))
Example 2	4.30	>500
Example 3	14.5	>500
Example 4	24.6	330

Table 1 (continued)

Test compound	ID_{50} (μg/ml)	Cytotoxity (CD_{50}(μg/ml))
Example 5	78.0	>500
acyclovir	0.80	>500

Example 8 :

Anti-viral activity against varicella zoster virus:

[0039] The activity of test compounds against varicella zoster virus was measured by plaque reduction assay. Confluent monolayers of human embryonic lung (HEL) cells grown in 6-well plates were infected with varicella zoster virus (Kawaguchi strain) in such a way that each well might have 100 plaqueforming units. After incubated at 37 °C for one hour in 5 % CO_2 atomosphere, the inoculum was removed and 3 ml of maintenace media containing the test compound having a varying concentration was added thereto. The incubation was continued for 3 days. After incubation, the cells were fixed and stained, the number of plaques was counted microscopically. In comparison to the control, the 50 % plaque decrease concentration (PI_{50}) of the test compound was determined. The PI_{50} value of each compound was shown in Table 2. As a comparative compound, acyclovir was used.

Table 2

Test compound	PI_{50} (μg/ml)
Example 2	0.07
Example 3	0.031
Example 5	0.054
Example 6	87
acyclovir	4.1

Example 9:

Preparation of a formulation for injection and eye drops:

[0040] One g of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione wad dissolved in 600 ml of distilled water, and filtered by a Millipore filter for sterilization. 15 g of the filtrate were put in a 20 ml-vial and lyophilized to obtain a freeze-dried preparation containing 25 mg/vial of the compound.

Example 10:

Preparation of a formulation of tablets:

[0041] 10 g of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione, 40 g of lactose, 49 g of crystalline cellulose and 1 g of magnesium stearate were well mixed and formed into tablets, using a tabletting machine. The tablets contained 250 mg/tablet of the active ingredient.

Example 11:

Preparation of a formulation of granules:

[0042] 10 g of 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione, 90 g of lactose and 100 g of crystalline cellulose were well mixed, compressed, using a roll compressor, powdered and sieved to obtain granules of 20 to 80-mesh.

Claims

1. A cyclopropane derivative selected from:

   (i) 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl] methyl-5-[(E)-2-chloroethenyl]-2,4(1H,3H)-pyrimidinedione;

   (ii) 1-[1'S,2'R-bis(hydroxymethyl)cyclopropan-1'-yl] methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione;

   (iii) 1-[1'S, 2'R-bis(hydroxymethyl) cyclopropan-1'-yl] methyl-5-[(E)-2-iodoethenyl]-2,4(1H,3H)-pyrimidinedione;

   (iv) 1-[1'α, 2'β-bis (hydroxymethyl) cyclopropan-1'-yl]methyl-5-[(E)-2-bromoethenyl]-2,4(1H,3H)-pyrimidinedione;

   (v) derivatives of (i) to (iv) wherein one or both hydroxyl groups independently are in the form of an ester with an acyl group having 1 to 6 carbon atoms, or with an acyl group having 1 to 6 carbon atoms substituted with a cycloalkyl group or aryl group;

   and pharmaceutically acceptable salts thereof.

2. A cyclopropane derivative selected from compounds (i) to (iv) of claim 1 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a cyclopropane derivative or a pharmaceutically acceptable salt thereof according to claim 1 or claim 2 and a pharmaceutically acceptable excipient, diluent or carrier.

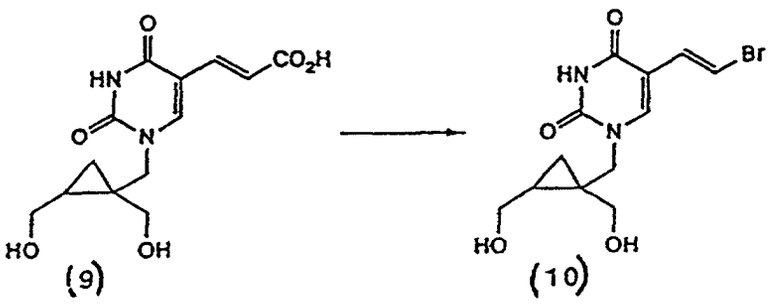
4. A cyclopropane derivative, or pharmaceutically acceptable salt thereof, according to claim 1 or claim 2 for pharmaceutical use.

5. Use of a cyclopropane derivative, or pharmaceutically acceptable salt thereof according to claim 1 or claim 2 in the manufacture of a medicament for the treatment of a viral infection.

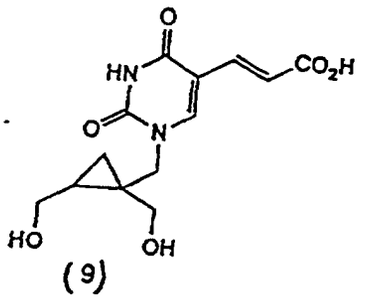
6. A method for the production of a compound of claim 2, comprising deprotection of a protected form of a compound of claim 2, said protected form having a protecting group for hydroxyl groups at each hydroxymethyl group.

7. A method for the production of a compound (v) of claim 1 in the form of an ester comprising acylation of a compound of claim 1 ((i)-(iv))containing two free hydroxymethyl groups.

8. A method for the production of a compound designated (ii) in claim 1 comprising decarboxylation- bromination of a compound of formula (9) to produce a compound of formula (10)



9. 1-[1'S,2'R-bis(hydroxymethyl) cyclopropan-1'yl] methyl-5-[(E)-2-carboxyethenyl]-2,4(1H,3H)-pyrimidinedione of formula(9).



(9)

Patentansprüche

1. Cyclopropanderivat, das ausgewählt ist unter

   (i) 1-[1'S, 2'R-Bis(hydroxymethyl)cyclopropan-1'-yl]-methyl-5-[(E)-2-chlorethenyl]-2,4(1H,3H)-pyrimidindion;

   (ii) 1-[1'S, 2'R-Bis(hydroxymethyl)cyclopropan-1'-yl]-methyl-5-[(E)-2-bromethenyl]-2,4(1H,3H)-pyrimidindion;

   (iii) 1-[1'S, 2'R-Bis(hydroxymethyl)cyclopropan-1'-yl]-methyl-5-[(E)-2-iodethenyl]-2,4(1H,3H)-pyrimidindion;

   (iv) 1-[1'α, 2'β-Bis(hydroxymethyl)cyclopropan-1'-yl]-methyl-5-[(E)-2-bromethenyl]-2,4(1H,3H)pyrimidindion;

   (v) Derivaten von (i) bis (iv), worin eine oder beide Hydroxylgruppen unabhängig voneinander in Form eines Esters mit einer Acylgruppe mit 1 bis 6 Kohlenstoffatomen oder mit einer Acylgruppe mit 1 bis 6 Kohlenstoffatomen, die durch eine Cycloalkylgruppe oder eine Arylgruppe substituiert ist, vorliegen,

   und pharmazeutisch geeignete Salze davon.

2. Cyclopropanderivat, das unter Verbindungen (i) bis (iv) gemäß Anspruch 1 ausgewählt ist, oder pharmazeutisch geeignetes Salz davon.

3. Arzneimittelzusammensetzung, enthaltend ein Cyclopropanderivat oder ein pharmazeutisch geeignetes Salz davon nach Anspruch 1 oder Anspruch 2 und ein pharmazeutisch geeignetes Streckmittel, Verdünnungsmittel oder Trägermaterial.

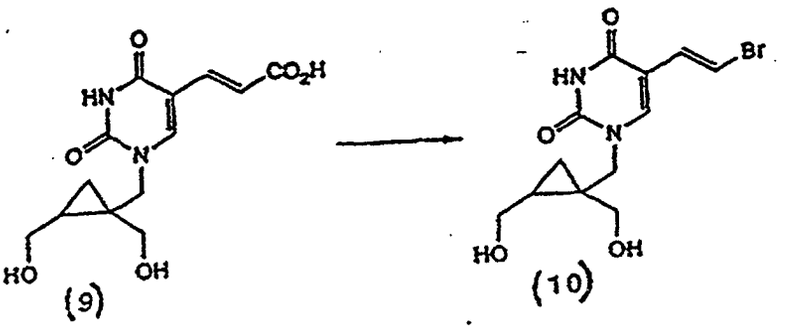
4. Cyclopropanderivat oder pharmazeutisch geeignetes Salz davon gemäß Anspruch 1 oder Anspruch 2 zur pharmazeutischen Verwendung.

5. Verwendung eines Cyclopropanderivats oder eines pharmazeutisch geeigneten Salzes davon gemäß Anspruch 1 oder Anspruch 2 zur Herstellung eines Arzneimittels zur Behandlung einer Virusinfektion.

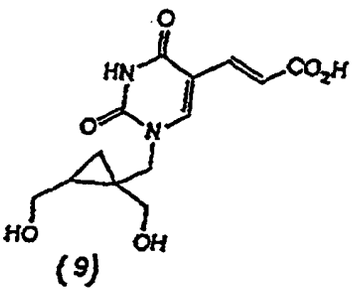
6. Verfahren zur Herstellung einer Verbindung nach Anspruch 2, welches das Entfernen der Schutzgruppe aus einer geschützten Form einer Verbindung nach Anspruch 2 umfaßt, wobei die geschützte Form eine Schutzgruppe für Hydroxylgruppen an jeder Hydroxymethylgruppe aufweist.

7. Verfahren zur Herstellung einer Verbindung (v) nach Anspruch 1 in Form eines Esters, welches die Acylierung einer Verbindung aus Anspruch 1 ((i)-(iv)), wie zwei freie Hydroxymethylgruppen enthält, umfaßt.

8. Verfahren zur Herstellung einer in Anspruch 1 als (ii) bezeichneten Verbindung, welches die Decarboxylierung-Bromierung einer Verbindung der Formel (9) unter Bildung einer Verbindung der Formel (10) umfaßt



9. 1-[1'S,2'R-Bis(hydroxymethyl)cyclopropan-1'yl]methyl-5-[(E)-2-carboxyethenyl]-2,4(1H,3H)-pyrimidindion der Formel (9)



Revendications

1. Dérivé de cyclopropane choisi parmi :

(i) 1-[1'S, 2'R-bis(hydroxyméthyl) cyclopropane-1'-yl]méthyl-5-[(E)-2-chloroéthényl]-2,4(1H, 3H)-pyrimidine ;
(ii) 1-[1'S, 2'R-bis (hydroxyméthyl) cyclopropane-1'-yl]méthyl-5-[(E)-2-bromoéthényl]-2,4(1H, 3H)-pyrimidine ;
(iii) 1-[1'S, 2'R-bis(hydroxyméthyl)cyclopropane-1'-y1]méthyl-5-[(E)-2-iodoéthényl]-2,4(1H, 3H)-pyrimidine ;
(iv) 1-[1'α, 2'β-bis(hydroxyméthyl)cyclopropane-1'-yl]méthyl-5-[(E)-2-bromoéthényl]-2,4(1H, 3H)-pyrimidine ;
(v) dérivés de (i) à (iv) dans lesquels l'un ou les deux groupes hydroxyles sont indépendamment sous la forme d'un ester avec un groupe acyle ayant 1 à 6 atomes de carbone ou, avec une groupe acyle ayant 1 à 6 atomes de carbone substitués par un groupe cycloalkyle ou un groupe aryle ;

et des sels de ceux-ci pharmaceutiquement acceptables.

2. Dérivé de cyclopropane choisi parmi les composés (i) à (iv) selon la revendication 1 ou un sel de ceux-ci pharmaceutiquement acceptable.

3. Composition pharmaceutique comprenant un dérivé de cyclopropane ou sel de celui-ci acceptable médicalement selon les revendications 1 ou 2 et un excipient, diluant ou entraîneur acceptable médicalement.

4. Dérivé de cyclopropane ou, sel de celui-ci acceptable médicalement, selon les revendications 1 ou 2, à usage pharmaceutique.

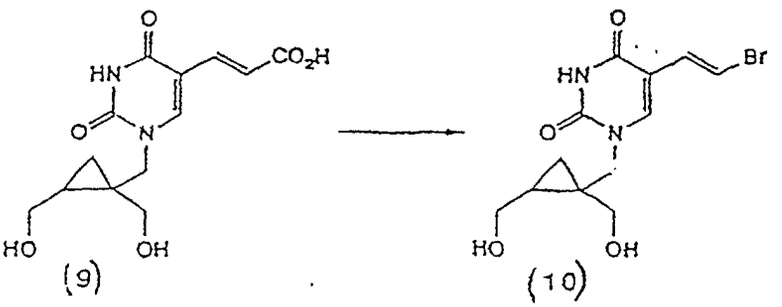
5. Utilisation d'un dérivé de cyclopropane ou, d'un sel de celui-ci pharmaceutiquement acceptable, selon les revendications 1 ou 2 pour la fabrication d'un médicament pour le traitement d'une infection virale.

6. Procédé de production d'un composé selon la revendication 2, comprenant une déprotection d'une forme protégée d'un composé selon la revendication 2, ladite forme protégée ayant un groupe de protection pour les groupes

hydroxyles au niveau de chacun des groupes hydroxyméthyles.

7. Procédé de production d'un composé (v) selon la revendication 1 sous la forme d'un ester comprenant l'acylation d'un composé selon la revendication 1 ((i)-(iv)) comprenant deux groupes hydroxyméthyles libres.

8. Procédé de production d'un composé désigné (v) dans la revendication 1 comprenant la décarboxylation-bromuration d'un composé de la formule (9) afin de produire un composé de la formule (10)



9. 1-[1'S, 2'R-bis(hydroxyméthyl)cyclopropane-1'-yl]méthyl-5-[(E)-2-carboxyéthényl]-2,4(1H, 3H)-pyrimidine de la formule (9).